EXHIBIT A71

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Chromium, Nickel and Welding

VOLUME 49

IARC, Lyon, France

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This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

5–13 June 1989

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IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. In 1980 and 1986, the programme was expanded to include the evaluation of the carcinogenic risk associated with exposures to complex mixtures and other agents.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed, and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

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NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups, in 1972, 1975, 1979, 1982 and 1987 (IARC, 1973, 1976, 1979, 1982, 1987). Since that time, new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Chemical and Physical Data

The list of nickel alloys and compounds given in Table 1 is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially and those that have been tested in biological systems. A number of intermediary compounds occur in refineries which cannot be characterized and are not listed.

1.1 Synonyms, trade names and molecular formulae of nickel and selected nickel-containing compounds

Table 1. Synonyms (Chemical Abstracts Service names are given in bold), trade names and atomic or molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Metallic nickel and nickel alloys				
Nickel	7440-02-0 (8049-31-8; 17375-04-1; 39303-46-3; 53527-81-4; 112084-17-0)	C.I. 77775; N1; Ni 233; Ni 270; Nickel 270; Nickel element; NP 2	Ni	0

Groups of 40 and 20 male Wistar rats, five weeks of age, were exposed by inhalation to 60 and 200 μg/m³ nickel as nickel monoxide aerosol (particle size, <0.3 μm) continuously for 18 months, followed by an observation period of one year under normal atmospheric conditions. At 24 months, 80% of animals in the treatment group had died, and at termination of the study (30 months) 62.5% of controls had died. No carcinogenic effect was observed (Glaser *et al.*, 1986). [The Working Group noted that the toxic effects, particularly alveolar proteinosis, were severe, that the survival of the animals was too short for carcinogenicity to be evaluated fully, and that nickel oxide aerosols were generated by atomization of aqueous nickel acetate solutions.]

Hamster: A group of 51 male Syrian golden hamsters, two months of age, was exposed by inhalation to a mean aerosol concentration of 53.2 mg/m³ nickel monoxide (mean particle diameter, 0.3 μm) for 7 h per day on five days per week for life. Another group of 51 males was exposed to nickel monoxide plus cigarette smoke. Two control groups of 51 animals were exposed to smoke and sham dust or to sham smoke and sham dust. Massive pneumoconiosis with lung consolidation developed in the nickel monoxide-exposed animals but did not affect their lifespan. Mean lifespan was 19.6 ± 1.6 months for animals exposed to smoke and nickel monoxide, 16.1 ± 1.1 for sham-exposed nickel oxide-treated animals and 19.6 ± 1.4 and 15.3 ± 1.3 months for the respective controls. No significant increase in the incidence of respiratory tumours or any evidence of cocarcinogenic interaction with cigarette smoke was noted for nickel monoxide. One osteosarcoma occurred in the nickel monoxide-treated group and one osteosarcoma and one rhabdomyosarcoma in the muscle of the thorax were seen in the group given nickel monoxide plus cigarette smoke (Wehner *et al.*, 1975, 1979).

(ii) *Intratracheal instillation*

Rat: Groups of female Wistar rats [numbers unspecified], 11 weeks of age, received ten weekly intratracheal instillations of 5 or 15 mg nickel as nickel monoxide (99.99% pure) in 0.3 ml saline to give total doses of 50 and 150 mg nickel, respectively. A control group of 40 rats received injections of saline only and were observed for 124 weeks. Lung tumour incidence in the two treated groups was 10/37 (27%) and 12/38 (31.6%), respectively; the tumours in the two groups consisted of four adenocarcinomas, two mixed tumours and 16 squamous-cell carcinomas. No lung tumour occurred in controls (Pott *et al.*, 1987).

Hamster: In an experiment designed to study the effects of particulates on the carcinogenesis of *N*-nitrosodiethylamine, groups of 25 male and 25 female hamsters [strain unspecified], five weeks old, received intratracheal instillations of 0.2 ml of a suspension of 2 g nickel monoxide (particle size, 0.5-1.0 μm) in 100 ml 0.5% w/v gelatin/saline once a week for 30 weeks. A group of 50 controls received injections

of carbon dust in the vehicle. Only three hamsters in each group survived beyond 48 weeks. One respiratory tract tumour [unspecified] was found in the 47 nickel monoxide-treated animals that were necropsied and four in controls. A high incidence of respiratory-tract tumours was observed in animals treated with *N*-nitrosodiethylamine alone (Farrell & Davis, 1974). [The Working Group noted the poor survival of treated and control animals.]

(iii) *Intrapleural administration*

Rat: A group of 32 male Wistar rats, three months of age, received a single intrapleural injection of 10 mg nickel monoxide in 0.4 ml saline suspension. A positive control group of 32 rats received a 10 mg injection of crocidolite, and a negative control group of 32 rats received saline alone. After 30 months, 31/32 rats in the nickel monoxide-treated group had developed injection-site tumours (mostly rhabdomyosarcomas). Median survival time was 224 days. Nine of 32 rats in the crocidolite-treated group had local tumours, but none of the saline controls developed local sarcomas (Skaug *et al.*, 1985).

(iv) *Intramuscular administration*

Mouse: Two groups of 50 Swiss and 52 C3H mice, equally divided by sex, two to three months of age, received single intramuscular injections of 5 mg nickel monoxide in penicillin G procaine into each thigh muscle and were observed for up to 476 days. Local sarcomas (mainly fibrosarcomas) occurred in 33 Swiss and 23 C3H mice. No control was reported (Gilman, 1962).

Rat: A group of 32 Wistar rats [sex unspecified], two to three months of age, received single intramuscular injections of 20 mg nickel monoxide powder into each thigh muscle and were observed for up to 595 days. Twenty-one rats developed a total of 26 tumours at the site of injection; 80% of the tumours were rhabdomyosarcomas, and the average latent period was 302 days. No control was reported (Gilman, 1962).

Groups of 20 Fischer rats [sex and age unspecified] received single intramuscular injections at two sites of either nickel hydroxide or nickel monoxide [dose unspecified] in aqueous penicillin G procaine. Local sarcomas developed in 15/20 (19 tumours at 40 sites) and 2/20 rats, respectively. Concurrent vehicle controls were not used. Seventeen of 20 animals given nickel subsulfide [dose unspecified] as positive controls developed local sarcomas. No tumour developed at the injection sites in two other groups of rats in the same experimental series injected intramuscularly with either nickel sulfate or nickel sulfide [presumed to be amorphous] (Gilman, 1966).

Ten male and ten female Wistar rats, weighing 150-170 g, received an intramuscular injection of 3 mg nickel trioxide powder. No control group was reported. No neoplasm developed at the injection site (Sosiński, 1975).